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Family Functioning as a Moderator of Neurocognitive Outcome Among Survivors of Acute Lymphoblastic Leukemia

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Family Functioning as a Moderator of Neurocognitive Outcome Among Survivors of Acute Lymphoblastic Leukemia

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Family Functioning as a Moderator of Neurocognitive Outcome Among Survivors of Acute Lymphoblastic Leukemia

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Evidence from the pediatric traumatic brain injury and pediatric brain tumor populations suggests that positive family functioning serves as a protective factor for neurocognitive outcomes of children who survive these conditions. However, no research has been found that examines whether positive family functioning similarly moderates the effects of CNS-directed chemotherapy on the neurocognitive functioning of survivors of pediatric ALL. The purpose of this study is to examine the effect of family functioning upon neurocognitive outcome among survivors of pediatric ALL treated with chemotherapy. Based upon a multidimensional model of attention and Anderson's model of executive function (EF), four subcomponents of attention (selective, divided, sustained, and shifting) and four subcomponents of EF (working memory, planning, inhibition, and processing speed) will be examined. Sequential, or hierarchical, multiple regression analyses will be conducted to examine the relationship between family functioning and neurocognitive functioning among survivors of pediatric ALL as well as a comparison group of healthy children. Data for the ALL group and the comparison group will be examined using separate analyses, with demographic and treatment-related variables entered first, followed by a family functioning variable. For the ALL group,

family functioning is expected to explain a significant amount of variance in neurocognitive outcome, even after controlling for demographic and treatment-related variables. It is expected that this relationship will not be found for the comparison group. If so, this would have important implications for the survivors and their families. For example, survivors from families with lower levels of functioning could be identified early through screening measures and their families could receive targeted interventions aimed at improving family functioning and thus survivor outcomes.

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Chapter One: Introduction

The most common form of cancer among children and adolescents is Acute Lymphoblastic Leukemia (ALL; Bisen-Hersh, Hineline, & Walker, 2011). Due to improvements in treatment regimens over the past forty years, over 80% of children diagnosed with ALL now survive (Winick, 2011). However, it has been found that the various treatment methods used in treating ALL can lead to deficits in a variety of neurocognitive domains (Winick, 2011). Together, these deficits are known as "neurocognitive late effects" (Mulhern & Palmer, 2003). While the use of chemotherapy instead of radiation therapy has helped to decrease the neurocognitive late effects experienced by survivors of ALL, research has found that chemotherapy-only treatment can still cause subtle neurocognitive late effects (Anderson & Kunin-Batson, 2009). Specifically, the areas of attention, executive function, visual-processing, and visual-motor integration have been found to be consistent areas of weakness among survivors of ALL treated with chemotherapy only (Buzier, de Sonneville, & Veerman, 2009). While these weaknesses are typically less pronounced than the weaknesses observed among survivors of ALL treated with radiation therapy, they still have important consequences for the survivors' lives after cancer (Anderson & Kunin-Batson, 2009).

As researchers gain a better understanding of the neurocognitive late effects associated with chemotherapy-only protocols for the treatment of childhood ALL, emphasis in research is now shifting towards the identification of variables that may serve to moderate or protect against the neurocognitive late effects (Daly, Kral, & Brown,

2008; Mulhern & Palmer, 2003). Some have suggested that psychosocial variables such as family functioning may moderate neurocognitive outcome among survivors of pediatric cancer (Anderson & Kunin-Batson, 2009).

In the field of traumatic brain injury, research suggests that the level of family functioning influences how well a child or adolescent recovers from neurocognitive insult (Max et al., 1999; Nadebaum, Anderson, & Catroppa, 2007; Taylor et al., 1999; Yeates et al., 1997). One study has investigated this phenomenon among survivors of pediatric brain tumors and found similar results (Carlson-Green, Morris, & Krawiecki, 1995). However, no research has been found that examines whether family functioning plays the same moderating role in the ALL population. The purpose of this study is to investigate whether family functioning moderates neurocognitive functioning following chemotherapy treatment for ALL. It is hypothesized that survivors of ALL from poorer functioning families will experience more severe neurocognitive late effects than those from higher functioning families.

Chapter Two: Integrative Analysis

Acute Lymphoblastic Leukemia

Prevalence.

Childhood cancer, although relatively rare, is more common than many people realize and is a significant health problem around the world (Moore, 2005; Riccio, Sullivan, & Cohen, 2010). Approximately 1 out of every 300 children under the age of 16 has cancer (Riccio et al., 2010). On average, one to two out of every 10,000 children is diagnosed with cancer each year in the United States (Moore, 2005; Butler & Haser, 2006). For example, approximately 10,400 children under the age of 15 were diagnosed with cancer in the United States in 2007, and approximately 1,545 children died from the disease that year (Riccio et al., 2010). Cancer is the leading cause of death by disease among children under the age of 15 and the second leading cause of death among children and adolescents overall, with accidents the first (Moore, 2005; Riccio et al., 2010).

The incidence of childhood cancer varies by age and by type of cancer, with some cancers more common at certain ages than others (Riccio et al., 2010). In general, the types of cancer most often seen in children are quite different from those common among adults (Riccio et al., 2010). Types of cancer commonly seen in children and adolescents are "leukemias, brain and other nervous system tumors, lymphomas (lymph node cancers), bone cancers, soft tissue sarcomas, kidney cancers, eye cancers, and adrenal gland cancers (American Cancer Society [ACS], 2006)" (Riccio et al., 2010, p. 207), with leukemias and solid tumors most prevalent in this age group (Riccio et al., 2010).

Leukemias are the most common form of cancer among children and adolescents, accounting for approximately one-third of cancers in children under the age of 15 and

one-fourth of cancers in people under the age of 20 (Butler & Haser, 2006; Riccio et al., 2010; Bisen-Hersh et al., 2011). Leukemia refers to a diverse set of diseases of the blood forming tissues (Brown et al., 1992; Daly, et al., 2008; Riccio et al., 2010). Leukemia is characterized by the production of large amounts of abnormal early-stage white blood cells called leukocytes (Daly, et al., 2008; Riccio et al., 2010). The leukocytes block production of normal white blood cells and therefore impede the child's ability to fight off infection (Daly, et al., 2008; Riccio et al., 2010). There are two types of normal white blood cells in which leukemia may develop: lymphoid cells and myeloid cells (U.S. Department of Health and Human Services, 2008). Leukemias that begin in lymphoid cells are referred to as lymphocytic, or lymphoblastic, leukemias; leukemias that begin in myeloid cells are referred to as myelogeneous, or myeloblastic, leukemias (U.S. Department of Health and Human Services, 2008). Leukemia can also be classified as either acute or chronic, depending on the speed with which the disease develops and progresses (U.S. Department of Health and Human Services, 2008). Acute leukemias are those that progress quickly, whereas chronic leukemias progress more slowly (U.S. Department of Health and Human Services, 2008). Altogether, then, there are four main types of leukemia: acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia (Riccio et al., 2010; U.S. Department of Health and Human Services, 2008).

The most common form of leukemia among children is acute lymphocytic leukemia (ALL), which is also known as acute lymphoblastic leukemia (Butler & Haser, 2006). ALL accounts for at least 75% of all cases of pediatric leukemia and approximately 25% of all childhood cancers overall (Butler & Haser, 2006; Mulhern & Butler, 2006; Riccio et al., 2010, Winick, 2011). This makes ALL the most common cancer of childhood and adolescence (Ashford et al., 2010; Kesler, Tanaka, &

Koovakkattu, 2010; Bisen-Hersh et al., 2011). Of the approximately 4,000 cases of ALL diagnosed annually in the United States, roughly two-thirds of these are among children and adolescents (Ashford et al., 2010). ALL occurs across ethnic groups but is slightly more prevalent among Caucasian children than among African American or Asian American children (Mulhern & Butler, 2006; Riccio et al., 2010). The yearly incidence of ALL among white children is about 3 or 4 per 100,000 (Mulhern & Palmer, 2003; Mennes et al., 2005). It is more common among boys than girls, with 1.3 males diagnosed for every 1 female diagnosed (McNeil, Cote, Clegg, & Mauer, 2002; Mulhern & Butler, 2006). The majority of cases of ALL are diagnosed in children between the ages of 2 to 5 years (Daly et al., 2008; Mulhern & Butler, 2006; Riccio et al., 2010).

Characteristics of ALL.

ALL is a "malignant disorder of lymphoid cells" that "results when a surplus of stem cells develop into lymphocytes, a type of white blood cell also referred to as leukemic cells" (Bisen-Hersh et al., 2011, p. 293). Lymphocytes are unable to fight infection and the proliferation of them leaves less room for healthy blood cells and platelets to form (Bisen-Hersh et al., 2011). The lymphocytes are originally found in the bone marrow (Mulhern & Butler, 2006). From there they enter the bloodstream and are transported, via the circulatory system, to nearly every organ system in the body (Bisen-Hersh et al., 2011; Mulhern & Butler, 2006). This includes the central nervous system (CNS), which consists of the brain and the spinal cord (Carlson, 2010). Possible genetic, environmental, and viral influences have been identified (Bisen-Hersh et al., 2011; Mulhern & Butler, 2006). For example, children with the genetic disorder Down syndrome have been found to be at an increased risk for the development of leukemia (Riccio et al., 2010). However, the genetic and environmental influences that have been

identified as implicated in the development of ALL so far do not account for the majority of cases of the disease and the exact causes of most cases of ALL remain unknown (Daly et al., 2008; Riccio et al., 2010; Bisen-Hersh et al., 2011).

Presenting symptoms of ALL can include fever, fatigue, paleness of the skin, bone pain, easy bleeding or bruising, infection, swelling of the abdomen, swollen lymph nodes, enlargement of the thymus gland, headache, seizures, vomiting, rashes, gum problems, and/or weakness (Mulhern & Butler, 2006; Riccio et al., 2010). Since many of these symptoms resemble those of a number of nonmalignant conditions, definitive diagnosis is based upon a combination of laboratory tests and imaging results and is sometimes delayed (Mulhern & Butler, 2006; Riccio et al., 2010). The specific laboratory tests used to diagnosis ALL include blood smear, bone marrow aspiration, bone marrow biopsy, spinal tap, and lymph node biopsy, with bone marrow aspiration being the most commonly used diagnostic test for this condition (Mulhern & Butler, 2006; Riccio et al., 2010). Once a child is diagnosed with ALL they are classified into one of four categories based upon the progression of the disease: low-risk, standard-risk, high-risk, and very high-risk (Riccio et al., 2010). This classification is made based upon the presence of cancer cells beyond the bone marrow and blood, in organs such as the liver, spleen, or lymph nodes (Riccio et al., 2010).

Treatment for ALL.

Treatment for ALL generally lasts for two to three years and consists of multiple phases (Bisen-Hersh et al., 2011; Moleski, 2000; Butler & Haser, 2006). Prior to the early 1960s, survival rates for ALL were very low (Moleski, 2000; Moore, 2005). However, survival rates have improved dramatically since that time due to marked improvements in the treatment of ALL (Butler & Haser, 2006; Winick, 2011). The factor most commonly credited as responsible for decreased mortality rates of ALL over the past several decades

has been the introduction of prophylactic CNS treatment, which prevents leukemia from spreading into the CNS (Buizer et al., 2009; Hill, Ciesielski, Sethre-Hofstad, Duncan, & Lorenzi, 1997; Von der Weid et al., 2003). CNS prophylaxis is necessary because the blood-brain barrier prevents chemotherapeutic agents delivered to the rest of the body from reaching the CNS (Buizer et al., 2009; Moleski, 2000). Without CNS prophylaxis the CNS is a sanctuary for leukemic cells and the chance of CNS relapse is high (Butler & Haser, 2006; Mennes et al., 2005; Mulhern & Palmer, 2003). CNS relapse, also known as CNS leukemia, occurs when leukemic cells invade and proliferate within the CNS (Brown et al., 1992; Moleski, 2000). Without CNS prophylaxis up to 80% of children and adolescents with ALL experience CNS relapse (Buizer et al., 2009). CNS relapse is a major cause of mortality in ALL (Buizer et al., 2009). The best way to treat CNS relapse is to prevent it from occurring, so CNS prophylaxis has become a standard part of treatment for children with ALL (Brown et al., 1992; Iuvone et al., 2002).

These new treatment protocols have served to nearly eliminate the occurrence of CNS relapse, which now occurs in less than 10% of cases of ALL (Buizer et al., 2009; Moleski, 2000). Currently, approximately 80% of children and adolescents diagnosed with ALL reach long-term event-free survivorship (Jansen et al., 2008; Waber et al., 2011). Survival rates are expected to rise to 90% in the next decade (Ashford et al., 2010; Bishen-Hersh et al., 2011).

Late effects of treatment.

With the increased survival rates that have accompanied improvements in the treatment of childhood ALL in the past several decades, interest has grown in the study of the "late effects" of CNS prophylactic treatment (Bisen-Hersh et al., 2011; Brouwers, 2005). Late effects are impairments in functioning that occur after the successful completion of cancer therapy (Mulhern & Butler, 2006). They are generally defined as

occurring two or more years after the time of diagnosis and are thus different from "acute effects", the "effects of disease and treatment that are acute or subacute and time limited, such as chemotherapy-induced nausea and vomiting or temporary cognitive changes induced by cancer therapy" (Mulhern & Butler, 2006, p. 262). Late effects are generally considered to be chronic and progressive (Mulhern & Butler, 2006). Among survivors of childhood cancer overall, approximately two-thirds experience at least one long-term consequence, or late effect, from their cancer and its treatment (Nathan et al., 2007).

Survivors of childhood ALL are especially at risk for long-term and progressive impairment in the area of cognitive functioning because CNS prophylaxis treatment can be toxic to the developing brain (Kesler et al., 2010; Nathan et al., 2007). The intellectual, academic, and neuropsychological deficits caused by CNS prophylactic treatment are known collectively as "neurocognitive late effects" (Daly et al., 2008; Espy et al., 2001).

The first form of CNS prophylactic treatment for ALL, introduced in the late 1960s and early 1970s, was cranial irradiation or cranial radiation therapy (CRT; Buizer et al., 2009; Montour-Proulx et al., 2005). At first, CRT consisted of 24 Gy of radiation delivered to the spinal cord (Buizer et al., 2009; Von der Weid et al., 2003). Although it served to significantly decrease the incidence of CNS relapse, and thus increased survival rates among children with ALL, research found a high incidence of neurocognitive deficits among survivors of ALL treated with CRT (Brown et al., 1992; Montour-Proulx et al., 2005). These included significant declines in overall intellectual functioning as well as impairments in short-term memory, attention, information processing, motor speed, and perception (Brown et al., 1992; Moleski, 2000). Furthermore, survivors of ALL treated with CRT were found to have an increased incidence of special education

placements for learning disabilities and to have decreased rates of secondary school completion (Mennes et al., 2005).

Based upon this research into the late effects of CRT, pediatric oncologists then began to explore ways to decrease the amount of CRT administered to children with ALL, while still ensuring survival. They began reducing the dosage of CRT (to 18 or even 12 Gy) and adding chemotherapy to the treatment protocols for childhood ALL (Buizer et al., 2009; Montour-Proulx et al., 2005). The chemotherapy was delivered intrathecally (directly into the spinal fluid) and typically consisted of the drug methotrexate (MTX), alone or in combination with other drugs (Brown et al., 1998; Buizer et al., 2009; Mulhern & Palmer, 2003). It was found that level of radiation could be reduced without negatively impacting CNS relapse-free survival rates, and a combination of CRT and intrathecal (IT) chemotherapy was the primary form of CNS prophylaxis for childhood ALL in the 1970s and early 1980s (Buizer et al., 2009; Kingma et al., 2002; Von der Weid et al., 2003). However, a high incidence of neurocognitive late effects persisted among survivors treated with combined modality (chemotherapy plus CRT) therapy, despite the decreased levels of radiation that were involved (Buizer et al., 2009; Kingma et al., 2002; Montour-Proulx et al., 2005).

In the mid-1980s, CRT was eliminated and chemotherapy-only treatment protocols began to be used as CNS prophylaxis for non-high-risk childhood ALL (Hill et al., 1997; Jansen et al., 2008; Kingma et al., 2002). It was found that similar, or even better, survival rates could be generated with chemotherapy-only treatment among children with standard-risk ALL (Buzier, de Sonneville, van den Heuvel-Eibrink, & Veerman, 2005; Moleski, 2000; Von der Weid et al., 2003). Currently, CRT is only used with children who are deemed to be at the highest risk for CNS disease, those who have CNS disease at the time of diagnosis, and those who experience CNS relapse (Kingma, et

al., 2002; Espy et al., 2001; Moleski, 2000). Typical CNS prophylaxis for non-high risk ALL now consists of systemic and IT chemotherapy, with or without intravenous MTX as well (Iuvone et al., 2002; Kingma et al., 2002; Montour-Proulx et al., 2005). Recent research has suggested that CRT may also be safely eliminated from treatment protocols for high-risk patients (Buizer et al., 2009). The specific chemotherapeutic agents used vary across medical institutions, but IT chemotherapy typically consists of MTX, alone or in combination with other drugs such as cytosine arabinoside (bytarabine), anthracyclines (such as doxorubicin), asparaginase, mercapclines, vincristine, and corticosteroids (Bisen-Hersh et al., 2011; Moleski, 2000).

Neurocognitive Late Effects of Chemotherapy

Given that chemotherapy-only protocols are now the standard form of CNS prophylaxis for the majority of children and adolescents with ALL, research interest in the neurocognitive late effects of this form of treatment has grown immensely over the past few decades (Buizer et al., 2009; Butler & Haser, 2006). Although there has been some inconsistency among the results of studies in this area, methodologically sound studies on the intellectual, academic, and neuropsychological functioning of ALL survivors treated with chemotherapy for CNS prophylaxis have shown that a significant amount of survivors show evidence of deficits in at least one area of functioning (Moleski, 2000; Peterson et al., 2008).

Intellectual functioning.

In terms of intellectual functioning, studies have found that survivors of childhood ALL treated with chemotherapy demonstrate impaired performance on measures of Full Scale IQ (FSIQ; Giralt et al., 1992; Hill et al., 1997; Raymond-Speden, Tripp, Lawrence, & Holdaway, 2000), Verbal IQ (VIQ; Giralt et al., 1992; Harila, Winqvist, Lanning, Bloigu, & Harila-Saari, 2009; Hill et al., 1997; Kingma et al., 2002; Raymond-Speden et

al., 2000), Performance IQ (PIQ; Brown et al., 1998; Giralt et al., 1992; Harila et al., 2009; Hill et al., 1997; Raymond-Speden et al., 2000), and Simultaneous Processing (Brown et al., 1992). Furthermore, some studies have found that children and adolescents receiving chemotherapy for CNS prophylaxis in ALL show evidence of declines in various areas of intellectual functioning over time after their treatment has ended. These areas include FSIQ (Mulhern, Fairclough, & Ochs, 1991; Ochs et al., 1991), VIQ (Harila et al., 2009; Mulhern et al., 1991; Ochs et al., 1991), and PIQ (Jansen et al., 2006; Montour-Proulx et al., 2005; Mulhern et al., 1991). However, other studies have found ALL survivors treated with chemotherapy-only to perform similarly to controls on measures of intellectual functioning (Anderson, Godber, Smibert, Weiskop, & Ekert, 2000; Ashford et al., 2010; Kingma et al., 2001; Rowland et al., 1984; Stehbens et al., 1994; Tamaroff et al., 1982; Ueberall et al., 1996; Von der Weid et al., 2003; Waber et al., 1995). Other studies found deficits in intellectual functioning relative to controls that approached, but did not reach, statistical significance (Carey et al., 2008; Kaemingk, Carey, Moore, Herzer, & Hutter, 2004; Reddick et al, 2006; Schatz, Kramer, Ablin, & Matthay, 2000).

In order to resolve these contradictions as to the presence or absence of deficits in intellectual functioning among ALL survivors treated with chemotherapy-only protocols, Moleski conducted an extensive review of the literature in 2000. Reviewing 33 studies published between 1981 and 1997, Moleski found that roughly two-thirds of the studies reported deficits in at least one area of intellectual functioning. Many of the studies that did not report finding evidence of impaired intellectual functioning among this population had significant methodological weaknesses (Moleski, 2000). In some of the studies, researchers reported that chemotherapy alone was not neurotoxic because the patients' mean IQ was in the average range. However, this conclusion is problematic

because research has found that healthy siblings of ALL survivors tend to function in the above average range of intellectual functioning, with an average IQ value of approximately 112 to 113 (Moleski, 2000). Therefore, it is reasonable to assume that the survivors themselves may have been functioning in the above average range as well if not for their treatment, and IQ scores in the lower end of the average range may in fact represent a decline in functioning for this population. Because of this, scholars have argued that is important to use matched controls, as opposed to normative data, for comparison when investigating neurocognitive late effects in this population (Moleski, 2000).

Some studies included in Moleski's seminal review of the literature enlisted a non-CNS treated cancer group in order to control for school absences due to treatment as well as for the psychological experience of having cancer (Moleski, 2000). All but one of these studies found evidence of impaired intellectual functioning among ALL patients receiving IT chemotherapy for CNS prophylaxis. Other studies used a healthy non-sibling control group for comparative purposes (Moleski, 2000). Two of these studies did not find evidence of declines in intellectual functioning among the subjects who had received chemotherapy. However, these two articles, which report on results from the same larger study, included both CNS- and non-CNS-treated cancer patients in their "chemotherapy-only" group. Therefore, no conclusions about the effects of chemotherapy used for CNS prophylaxis can be made, as the CNS-treated subjects were mixed with what should have been a non-CNS cancer control group. Another study that reported finding no evidence of declines in intellectual functioning among ALL survivors treated with chemotherapy had only 3 such subjects in its study (Moleski, 2000), a sample size that makes rendering conclusions for the larger population rather difficult. Overall, Moleski found that studies which had included a control group of either siblings or non-CNS-treated cancer patients

consistently found significant differences in intellectual functioning between the control groups and ALL survivors treated with chemotherapy.

Peterson and colleagues followed up Moleski's review of the literature with a meta-analysis in 2008. Criteria used for inclusion in the meta-analysis were: inclusion of participants who had competed chemotherapy-only treatment for pediatric ALL as well as a comparison group that did not receive CNS-directed treatment, publication in English, inclusion of enough original data to allow for calculation of effect sizes, and publication after 1990 (Peterson et al., 2008). Of the 160 relevant articles originally found, the majority failed to meet criteria for inclusion in the study and only 13 were included in the meta-analysis. The results of the analysis indicated that survivors of pediatric ALL treated with chemotherapy alone had significantly lower FSIQ scores as compared to control groups (Mean effect size = 0.55, 95% Confidence Interval = 0.27 – 0.83, n = 10). After eliminating from analysis the three studies that had used test norms as the control group and the three that utilized foreign translations of intelligence tests, the recalculated mean effect size for FSIQ from the remaining seven studies was still significantly different from zero (M = 0.76, 95% CI = 0.42 – 1.12, n = 7). Similar results were found for the index scores VIQ and PIQ and for subtests measuring working memory and processing speed as well. These results provide empirical support to the assertion that survivors of pediatric ALL treated with chemotherapy-only do experience deficits in intellectual functioning following their treatment.

Neuropsychological functioning.

Deficits in intellectual and academic functioning among this population have been well established in the literature (Mulhern & Palmer, 2003). Originally, it was thought that these deficits could be due to the general effects of chronic illness and school absenteeism (Mulhern & Palmer, 2003). However, studies involving control groups

comprised of pediatric cancer patients whose treatment did not include CNS directed chemotherapy have disproved this notion (Mulhern & Palmer, 2003). It is now believed that deficits in intellectual and academic functioning are "secondary" late effects resulting from deficits in what are called "core" areas of neuropsychological functioning, such as attention, working memory, processing speed, and memory (Bisen-Hersh et al., 2011; Schatz et al., 2000). It is thought that these deficits in core mental processes impair the development of higher-level abilities, leading to the declines in IQ level found among this population (Bisen-Hersh et al., 2011; Schatz et al., 2000).

The focus of research on neurocognitive late effects of chemotherapy among survivors of childhood ALL has shifted from the study of global intellectual functioning to the identification of patterns of specific neuropsychological deficits in this population (Butler & Haser, 2006; Moleski, 2000; Mulhern & Palmer, 2003). Evidence from these studies has shown that survivors of childhood ALL treated with chemotherapy alone consistently show declines in at least one area of "core" neuropsychological functioning (Moleski, 2000). The specific core neuropsychological domains most commonly affected in this population are attention and executive functioning (Anderson & Kunin-Batson, 2009; Buizer et al., 2009; Peterson et al., 2008). These basic neuropsychological processes are crucial for the acquisition of new information and skills, and deficits in these areas are thought to underlie poor performance of ALL survivors in the classroom and beyond (Buizer et al., 2009; Mulhern & Palmer, 2003).

Attention.

The domain of attention consists of a number of subdomains, including selective attention, divided attention, sustained attention, and shifting attention (Baron, 2004; Ginstfeldt & Emanuelson, 2010; Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991). Selective attention is the ability to maintain focus on a particular cognitive set or stimuli

"in the presence of background 'noise' or distraction" (Baron, 2004, p. 222). Commonly used tests of selective attention include digit span tasks, where participants are asked to repeat a sequence of numbers read to them by the examiner. Divided attention is the ability to "respond to more than one task or event simultaneously" (Baron, 2004, p. 222). Commonly administered tests of divided attention include trail making tests, in which the participant has to draw a line between circles while alternating between numbers and letters in sequence. Sustained attention is defined as the "ability to maintain vigilance and respond consistently during continuous or repetitive activity" (Baron, 2004, p. 223). Commonly administered tests of sustained attention include continuous performance tests, which require the subject to attend to a visual or auditory presentation of a series of random letters and to respond to a target stimulus. Finally, shifting attention is the ability to flexibly shift ones attention from one focus or stimuli to another (Baron, 2004). Commonly administered tests of shifting attention include verbal and design fluency tests, which detect difficulties with the ability to shift in terms of perseverative errors (Baron, 2004).

Survivors of ALL treated with chemotherapy alone have been found to demonstrate impairments in a variety of subdomains of attention. In fact, attention is one of the domains most commonly found to be impacted in studies of this population, with approximately one-fourth of survivors of ALL showing evidence of deficits in attention (Bisen-Hersh et al., 2011; Butler & Copeland, 2002). Specifically, studies have found evidence of impaired performance, relative to controls, on tests of selective (Ashford et al., 2010; Carey et al., 2008; Harila et al., 2009), divided (Carey et al., 2008; Kingma et al., 2002; Lesnik, Ciesielski, Hart, Benzel, & Sanders, 1998), sustained (Reddick et al., 2006), and shifting (Buizer et al., 2005) attention. These deficits may impact survivors' ability to maintain concentration and ignore distractions, which in turn may negatively

impact their academic achievement and quality of life (Anderson & Kunin-Batson, 2009; Butler & Copeland, 2002).

Executive functioning.

Executive functioning (EF) is a somewhat nebulous concept within the field of neuropsychology, as several differing definitions and models of EF have been proposed but none have received universal acceptance (Baron, 2004). Various subcomponents of EF that have been proposed include planning, reasoning, cognitive flexibility, inhibition, initiation, and working memory (Anderson, 2002; Baron, 2004). Further complicating the conceptualization and assessment of EF is the fact that various aspects of EF overlap considerably with other domains of neurocognitive functioning such as attention and memory (Baron, 2004). However, the abilities that fall under the domain of EF are crucial to successful daily living and consideration of their intactness among survivors of pediatric ALL is critical (Anderson, 2002; Baron, 2004).

Researchers have proposed a developmental model of executive functioning based upon factor analysis and clinical neuropsychological knowledge (Anderson, 2002). In this model, EF is comprised of four distinct domains, referred to as: (a) attentional control, (b) information processing, (c) cognitive flexibility, and (d) goal setting. Although these domains are thought to be separate within this model, they are also thought to operate in an integrative manner in order to execute tasks. Thus, they can be conceptualized of as an overall control system (Anderson, 2002). Each of these domains subsumes a number of highly integrated cognitive processes.

Within this model of EF, the attentional control domain relates to the ability to selectively attend to certain stimuli, to inhibit certain responses, and to focus attention for a prolonged period of time (Anderson, 2002). Therefore, it consists of processes such as selective attention, self-regulation, self-monitoring, and inhibition. Deficits in attentional

control are thought to be reflected by impulsive behavior, lack of self-control, failure to complete tasks, the inability to self-correct procedural mistakes, and inappropriate responses to stimuli or situation.

The information processing domain refers to the ability to quickly and accurately process information (Anderson, 2002). It is thought to include processes such as efficiency, fluency, and processing speed. Deficits in this domain are thought to be reflected by reduced output, delayed responses, hesitancy, and slow reaction times.

The goal setting domain refers to the ability to develop new initiatives and concepts, to plan actions in advance, and to approach tasks in an efficient and strategic manner (Anderson, 2002). Aspects of this domain include initiative, conceptual reasoning, planning, and strategic organization. Deficits in this domain are reflected by poor problem solving abilities, disorganization, poor planning, development of inefficient strategies, continued reliance on previously learned strategies even when they are no longer effective, and poor conceptual reasoning.

The cognitive flexibility domain refers to the ability to shift between cognitive sets, to learn from mistakes, to divide attention, to devise alternative strategies, and to simultaneously process multiple sources of information (Anderson, 2002). Components of this domain are divided attention, working memory, conceptual transfer, and feedback utilization. Deficits in this domain are reflected in rigidity and ritualistic behavior, difficulty with new activities or procedures, failure to adapt to new demands, and perseverative behavior such as continuing to make the same mistake or break the same rule regardless of feedback.

Studies have found that survivors of pediatric ALL treated with chemotherapy-only show evidence of deficits, relative to controls, in various aspects of executive functioning. These include cognitive flexibility/working memory (Ashford et al., 2010;

Carey et al., 2008; Kingma et al., 2002; Lesnik et al., 1998; Waber et al., 1995), information processing/processing speed (Jansen, 2008), and attentional control/inhibition (Harila et al., 2009). These deficits have been found to underline problems with behavior and school performance among survivors of ALL treated with chemotherapy-only protocols (Buizer et al., 2009). Furthermore, deficits in executive functioning have implications for survivors' long-term occupational and social functioning and their overall quality of life (Campbell et al., 2007).

Summary.

Overall, research shows that chemotherapy-only treatment for ALL, while perhaps less neurotoxic than CRT, is still associated with neurocognitive late effects (Riccio et al., 2010; Winick, 2011). Deficits in the areas of attention and executive functioning are particularly prevalent among this population (Anderson & Kunin-Batson, 2009; Campbell et al., 2007; Peterson et al., 2008; Riccio et al., 2010; Winick, 2011). These deficits may lead to real and significant impairments in the classroom setting (Nathan et al., 2007). Impairments in attention and executive functions such as working memory, cognitive flexibility, and inhibition have also been found to be associated with increased stress and problem behavior and decreased ability to use effective coping strategies among survivors of pediatric ALL, all of which impact the survivors' quality of life (Riccio et al., 2010).

Risk and protective factors.

As understanding of the neurocognitive late effects of chemotherapy-only treatment for ALL improves, a prominent focus of research has become the risk and protective factors that serve to mediate and moderate the effects of the treatment. Traditionally the focus of this research has been on biologic moderators and mediators, including disease and treatment-related factors such as the intensity of the treatment

regimen (Brouwers, 2005; Buizer et al., 2009). Children who have received intensified treatment, such as higher doses of systemic methotrexate, have been found to perform significantly worse than survivors treated on lower intensity protocols in a few studies (Buizer et al., 2005; Buizer et al., 2009). However, some studies examining differences in outcome based on risk-group and treatment intensity have found that these differences are less pronounced than those related to child characteristics such as age at diagnosis and maternal education level (Waber et al., 2011). Such findings suggest that a focus on child-related and psychosocial risk factors is increasingly important for this population.

Child-related moderators of neurocognitive outcome include age at diagnosis, gender, time since diagnosis, and age at testing (Brouwers, 2008). Specifically, young age at diagnosis and female gender have been found to be risk factors for neurocognitive late effects following chemotherapy-only treatment for ALL (Buizer et al., 2009; Moleski, 2000; Peterson et al., 2008). Particularly, children younger than 5 years of age at the time of diagnosis have been found to be particularly vulnerable to cognitive dysfunction as a result of their treatment (Buizer et al., 2009). This is believed to be due to the fact that their brains, being less mature than those of older children, are more vulnerable to the neurotoxicity of the treatments used for CNS prophylaxis (Buizer et al., 2009). In this case, age at treatment is seen as a proxy for the level of "neurodevelopmental maturity" of the child's brain (Mulhern & Palmer, 2003). Several studies have found that male survivors of pediatric ALL outperform female survivors on tests of neurocognitive functioning (Buizer et al., 2009). Effect-size statistics used in a meta-analysis on this literature confirmed the significance of the differential performances between male and female survivors (Peterson et al., 2008). Thus, girls appear to exhibit more late effects.

In addition to these child-related moderators, social and demographic moderators of neurocognitive outcome in this population have also been identified. Socioeconomic status (SES) has been identified as one such moderator in that differences in SES have been found to account for a significant amount of variability in neurocognitive outcome among this population (Stehbens et al 1994; Winick, 2011). Specifically, survivors of pediatric cancer from families with higher levels of SES have been found to have higher levels of neurocognitive functioning after treatment (Mulhern & Palmer, 2003).

Research has clarified our understanding of the medical, treatment-related, child-related, and demographic factors that mediate and moderate neurocognitive outcome in survivors of pediatric ALL (Patel & Carlson-Green, 2005). However, much less is known about potential psychosocial moderators of neurocognitive outcome in this population (Anderson & Kunin-Batson, 2009). One specific potential psychosocial moderator of neurocognitive outcome that has not yet been explored among survivors of pediatric ALL is that of family functioning. Given evidence from the pediatric traumatic brain injury and pediatric brain tumor fields as to the effect that family variables have on neurocognitive outcome, it is worth exploring whether positive family functioning serves as a protective factor against neurocognitive late effects for survivors of pediatric ALL (Anderson & Kunin-Batson, 2009; Hocking et al., 2011; Nathan et al., 2007).

Family Functioning

From a family systems perspective, family functioning refers to a family's ability to engage in basic interactional patterns that enable them to achieve family goals (Walsh, 2011). There are several models of family functioning, but most include dimensions such as "family structure or organization, communication, cohesion, problem solving, and emotional expression" (Hocking et al., 2011, p. 945). One model of family functioning that is used quite often in research and practice is the McMaster Model of Family

Functioning (MMFF), which was first described by Epstein, Bishop, and Levin in 1978 (Carlson, 2003; Epstein, Ryan, Bishop, Miller, & Keitner, 2003).

The McMaster Model of Family Functioning.

Grounded in systems theory, the MMFF views families as open systems that are comprised of various subsystems (i.e., parents, children) that relate to other, larger systems such as schools and extended family (Carlson, 2001; Epstein et al., 2003; Lebow & Stroud, 2011). Underlying the MMFF is the assumption that the primary purpose of the family unit is to facilitate the social, psychological, and biological growth and maintenance of its members (Epstein et al., 2003). According to this model, this purpose is achieved through the accomplishment of a variety of tasks, which the developers of the MMFF divide into three types: Basic Tasks, Developmental Tasks, and Hazardous Tasks (Epstein et al., 2003; Lebow & Stroud, 2011). Basic Tasks are the most fundamental and involve instrumental issues such as the provision of food, money, transportation, and shelter (Epstein et al., 2003). Developmental Tasks are the various stages that the family and its members face over time. These occur on both an individual level (i.e., infancy, childhood, adolescence, middle age, and old age) and a family level (i.e., the beginning of a marriage, a first pregnancy, or the "empty nest" after the last child leaves home; Epstein et al., 2003). Hazardous Tasks are crises that arise due to unexpected circumstances, such as accidents or job loss (Epstein et al., 2003). Inability for a family to effectively accomplish these three task areas has been found to be associated with the development of clinically significant problems and maladaptive family functioning (Epstein et al., 2003).

Dimensions of family functioning in the MMFF.

The MMFF identifies six dimensions of family functioning as being most important for the emotional and physical health of family members and the effective accomplishment of the tasks required of the family (Epstein et al., 2003; Lebow & Stroud, 2011). The six dimensions, which will be defined in greater detail, are: problem solving, communication, role functioning, affective responsiveness, affective involvement, and behavior control (Epstein et al., 2003; Lebow & Stroud, 2011). Within each dimension, the authors of the MMFF have identified practices and patterns of interaction that they deem to range from "most ineffective" to "most effective" (Epstein et al., 2003). "Most ineffective" functioning in a dimension is thought to lead to the development of clinically significant difficulties for the family, while "most effective" functioning in all dimensions is thought to contribute to "optimal physical and emotional health" among family members (Epstein et al., 2003, p. 582). Research on the MMFF has not found one dimension that serves to predict good or poor overall family functioning on its own; rather, all dimensions are thought to be important to understanding the overall function of a family (Epstein et al., 2003).

Problem solving.

Problem solving is defined within this model as the ability of a family to efficiently and easily resolve problems so as to maintain effective family functioning (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al., 2000). The MMFF identifies two types of problems that families face: instrumental and affective (Epstein et al., 2003). Instrumental problems are those that relate to the provision of basic necessities of living, whereas affective problems are those relating to emotions and feelings (Epstein et al., 2003).

In the MMFF, effective problem solving can be broken down into seven sequential steps: (1) problem identification, (2) communication about the problem with

appropriate people, (3) development of a set of possible solutions, (4) deciding which solution to pursue, (5) putting the solution into place, (6) monitoring the progress of solution implementation, and (7) evaluation of the effectiveness of the problem-solving process (Epstein et al., 2003). According to this theory, the process that a family engages in when faced with problems in need of solutions is more important than the content of those problems in determining the level of functioning of the family (Epstein et al., 2003). Highly functioning families tend to engage in these steps (discussing the issues, communicating with each other, deciding on and implementing an appropriate solution, etc.) whether the problem is relatively minor or is rather major, such as a job loss or terminal illness (Epstein et al., 2003).

The developers of the MMFF hypothesize that most effective functioning in this domain occurs when (a) both instrumental and affective problems are solved and (b) when all seven steps of the problem-solving process are preformed (Epstein et al., 2003). Least effective functioning is thought to occur when families are unable to complete even step one of the process, the identification of problems (Epstein et al., 2003).

Communication.

The second dimension of family functioning included in the MMFF is communication, which is defined within the model as the patterns of verbal information exchange that occur within the family (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al., 2000). The MMFF focuses on verbal, as opposed to nonverbal or behavioral, communication because it is more easily observed and measured (Epstein et al., 2003). Furthermore, it focuses on the overall family pattern of communication as opposed to examining the individual communication styles of members of the family, as this has been found to be most helpful to families and family therapists in the clinical experience of the authors of the MMFF (Epstein et al., 2003).

As with problem solving, the MMFF divides communication into two areas, instrumental and affective (Epstein et al., 2003). In addition, the MMFF considers the style of communication in which the family engages. It does so along two independent continua, with one ranging from clear to masked and the other ranging from direct to indirect (Epstein et al., 2003). The clear vs. masked continuum refers to whether the message is expressed clearly or is vague and muddy. The direct vs. indirect distinction refers to whether the message is expressed to the intended recipient or to another member of the family (Miller et al., 2000).

Therefore, within the MMFF there are considered to be four possible styles of communication: clear and direct, clear and indirect, masked and direct, and masked and indirect (Epstein et al., 2003). To illustrate each of these four possible styles, imagine a situation in which a wife is angry with her husband for coming home late from work without calling. An example of clear and direct communication in this circumstance would be if she told him "I am upset that you are late and I wish you would have called to tell me you would be late." An example of clear and indirect communication would be if the wife told their daughter, in the presence of the husband, "I am upset with your father because he was late and did not call to tell me that he would be." An example of masked and direct communication would be if the wife said to her husband "Traffic must have been really bad for you to be getting home at this time." Finally, an example of masked and indirect communication would be if the wife told the daughter, in the presence of her husband, "It's really annoying when I don't know what time people are planning to be home for dinner." Although the model focuses on verbal communication, it does take into account nonverbal behavior, especially in so far as it contradicts the information that is being verbally exchanged, as this is thought to reflect masking or indirectness or both (Epstein et al., 2003).

According to the MMFF, most effective functioning in this domain occurs when (a) the family is able to communicate well about both instrumental and affective matters and (b) when the communication is clear and direct (Epstein et al., 2003). Least effective functioning is thought to occur when the communication in the family is masked and indirect (Epstein et al., 2003).

Role functioning.

Within the MMFF, roles are defined as the patterns of behavior family members engage in so as to fulfill the family's functions (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al, 2000). According to the MMFF, there are five basic types of family functions that are necessary for the maintenance of an effective and healthy family system: provision of resources, nurturance and support, adult sexual gratification, personal development, and maintenance and management of the family system (Epstein et al., 2003). Each of these areas includes a number of tasks and functions. The 'provision of resources' area includes tasks and functions related to the attainment of food, clothing, shelter, and other basic human needs. The 'nurturance and support' area includes tasks related to providing members of the family with warmth, comfort, and reassurance. The 'adult sexual gratification' area involves ensuring that each adult partner is satisfied with the level of sexual intimacy present in the relationship. 'Personal development' tasks and functions include those related to the physical, emotional, educational, social, and professional development of each family member. Finally, the 'maintenance and management of the family system' area includes a variety of functions and tasks related to decision making/leadership, boundaries, finances, discipline, and health (Epstein et al., 2003).

The MMFF identifies two aspects of role functioning that are deemed to be vital to effective family functioning: role allocation and role accountability (Epstein et al.,

2003). Role allocation involves the family's patterns for the assignment of roles and role accountability refers to the ways in which the family ensures that roles are fulfilled (Epstein et al., 2003). An example is the task of taking out the trash, a part of the provision of resources area of family role functioning. The parents discussing amongst themselves who will be responsible for taking out the trash and deciding together that it will be their oldest son's job to do so would be an example of role allocation. The use of a sticker chart to monitor whether or not the son has accomplished this task would be an example of role accountability.

Most effective functioning occurs when all of the family functions have been clearly allocated to the appropriate family member(s) and when accountability is maintained (Epstein et al., 2003). Least effective functioning occurs when necessary family functions are unaddressed and when either allocation or accountability is not maintained (Epstein et al., 2003).

Affective responsiveness.

Affective responsiveness within the MMFF relates to the family's range of emotional responses to stimuli, both in terms of quality and quantity (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al., 2000). The qualitative aspect refers to the ability of the family to respond with a spectrum of human emotions, as well as whether or not the emotion experienced matches the stimuli and/or context (Epstein et al., 2003). The quantitative aspect refers to the degree of affective response expressed, and ranges from absence of response to over-responsiveness, with reasonable or expected responsiveness in the middle (Epstein et al., 2003). The MMFF identifies two groups of affect: welfare emotions (such as love, joy, and concern) and emergency emotions (such as sadness, fear, and anger; Epstein et al., 2003).

Most effective functioning is defined as occurring when the family experiences a full range of qualitatively and quantitatively appropriate responses to stimuli. Least effective functioning occurs when only a narrow range of affect is experienced or when the amount and quality of affective responses are inappropriate for the context in which they occur (Epstein et al., 2003).

Affective involvement.

The MMFF defines affective involvement as the degree to which the family demonstrates interest in and values the activities and interests of individual family members (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al., 2000). This dimension focuses both on the amount of interest the family shows as well as the way(s) in which they demonstrate that interest (Epstein et al., 2003). The model identifies six types of affective involvement: lack of involvement, involvement devoid of feelings, narcissistic involvement, empathic involvement, overinvolvement, and symbiotic involvement (Epstein et al., 2003). These types exist on a continuum, with 'lack of involvement' at one extreme and 'symbiotic involvement' at the other.

'Lack of involvement' occurs when family members have no interest or investment in one another's lives. 'Involvement devoid of feelings' is when family members have a purely intellectual interest in one another. 'Narcissistic involvement' occurs when a family member is only interested in another family member to the extent that the other member's behavior reflects upon themselves. 'Empathic involvement' takes place when family members' interest in each other is for the sake of the other person. 'Overinvolvement' happens when family members show an excessive amount of interest in one another. Finally, 'symbiotic involvement' occurs when family members are invested in one another to such an extreme and pathological extent that it is difficult to differentiate between the individual members of the family. Empathic involvement is

thought to contribute to most effective functioning in this dimension, with symbiotic involvement and absence of involvement leading to least effective functioning (Epstein et al., 2003).

Behavior control.

The final dimension of family functioning within the MMFF, behavior control, is the pattern of standards and rules set by the family in order to handle the behavior of its members in a variety of situations (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al., 2000). These situations are grouped into three types: physically dangerous situations, situations involving psychobiological needs, and situations that involve interpersonal socialization, both within and outside of the family (Epstein et al., 2003). Each of these types of situations may require different sets of standards and rules from the family.

In addition to the standards and rules set by the family in these areas, the MMFF is also interested in the amount of latitude that the family allows relative to these standards and rules (Epstein et al., 2003). Included in the model are four styles of behavior control that vary in terms of standards and latitude: rigid behavior control, flexible behavior control, laissez-faire behavior control, and chaotic behavior control (Epstein et al., 2003). Rigid behavior control occurs when the family's standards for behavior are quite narrow and specific and the family allows for very little variation or negotiation between situations. In flexible behavior control, the standards set by the family are reasonable and may vary or be negotiable depending on the context or situation. With laissez-faire behavior control, the family holds no standards for the behavior of its members, allowing members complete latitude regardless of the situation. Finally, a chaotic behavior control style consists of a random and unpredictable vacillation between the three previous styles of behavior control, such that members of the family never know what to expect. Most effective functioning is associated with a

flexible behavior control style and least effective functioning is associated with a chaotic behavior control style (Epstein et al., 2003).

Dimensions of family functioning among families of pediatric ALL survivors.

Consideration of family functioning is crucial to a comprehensive understanding of the experience of survivors of pediatric ALL because childhood cancer is in many ways a family affair (Alderfer, Navsaria, & Kazak, 2009; Butler & Copeland, 2006). A diagnosis of a potentially terminal illness such as ALL in a child poses a significant challenge to the functioning of that child's family (Alderfer et al., 2009). Families of children receiving cancer treatment have been found to demonstrate lower levels of functioning than families of children who have completed treatment, but even "off-treatment" families have been found to show evidence of long-term disruptions in family functioning (Alderfer et al., 2009).

Research examining family functioning among adolescent survivors of childhood cancer and their families has found higher levels of self-reported difficulties in family functioning among this population (Alderfer et al., 2009). One study that used a self-report measure of family functioning based on the MMFF found that 35-62% of adolescent survivors and 17-44% of their parents reported poor levels of family functioning in at least one of the six dimensions of the MMFF (Alderfer et al., 2009). In that study, almost half of the adolescent survivors, one fourth of their mothers, and one third of their fathers reported poor family functioning on four or more of the dimensions of family functioning included in the MMFF (Alderfer et al., 2009). These levels of self-reported difficulties with family functioning are much higher than are typically found among community samples, in which less than 10% report poor functioning on that many dimensions (Alderfer et al., 2009). This indicates that the six dimensions of family

functioning included in the MMFF are very relevant areas to consider when working with survivors of childhood ALL and their families.

Family functioning and neurocognitive late effects in traumatic brain injury.

Although the relationship between family functioning and neurocognitive functioning has not been studied among survivors of pediatric ALL, there is evidence from research on pediatric traumatic brain injury (TBI) that family variables, such as family functioning, may predict child neurocognitive outcomes following TBI (Hocking et al., 2011). Studies have found better family functioning to be positively associated with neurocognitive outcomes following pediatric TBI (Nadebaum, Anderson, & Catroppa, 2007). Researchers began investigating family influences on neurocognitive sequelae in pediatric TBI after it had been found that pediatric TBI has a negative impact on families (Taylor et al., 1999). It was thought that the negative impacts of TBI upon the family might in turn make it difficult for the family to adequately support the child's recovery from TBI (Taylor et al., 1999). Supporting this notion, there has been evidence linking family stress and ineffective parenting practices within the clinical literature (Taylor et al., 1999). Furthermore, studies performed on animals showed that environmental influences affected recovery of function (Taylor et al., 1999). Therefore, researchers in the field of pediatric TBI hypothesized that the long-term sequelae of pediatric TBI may be partially related to environmental factors such as family functioning (Taylor et al., 1999). As there have been no reviews or meta-analyses conducted on this literature to date, each study investigating the relationship between family functioning and neurocognitive outcome following pediatric TBI will be examined individually.

Yeates and colleagues (1997) examined the influence of injury severity and preinjury social environment on neurocognitive outcomes among children with severe TBI, moderate TBI, and a comparison group of children with orthopedic injuries (OI).

They assessed premorbid child and family characteristics during a baseline assessment shortly after the children's injuries and child neurocognitive functioning was assessed at baseline and approximately 6 and 12 months postinjury (Yeates et al., 1997). They used growth curve analysis to test three hypotheses regarding the influence of injury severity and pre-injury social environment on neurocognitive outcome (Yeates et al., 1997). The measures of pre-injury family environment, which were used a predictors of neurocognitive outcomes, included the Family Assessment Device (FAD), a measure of family functioning based upon the MMFF (Yeates et al., 1997). There were three measures of cognitive functioning chosen as dependent variables. The first was a prorated Performance Scale IQ (PIQ) derived from a short form of the Wechsler Intelligence Scale for Children – Third Edition (WISC-III), which was used as a measure of nonverbal skills that has been found to be sensitive to the acute effects of TBI in children. The second measure of cognitive functioning was the total raw score from the Developmental Test of Visual–Motor Integration (VMI), a drawing task that requires visuoperceptual, constructional, and graphomotor skills and has been shown to be sensitive to TBI in children. The final measure of cognitive functioning used was the total number of words recalled across five learning trials on a shortened, preliminary version of the children's California Verbal Learning Test (CVLT), a word-list learning task that measures verbal memory skills. Total recall on the CVLT has been shown to discriminate between children with TBI and matched controls.

Yeates and colleagues (1997) found that the four family variables included in their analysis accounted for significant amounts of variance in each of their outcome measures, even after controlling for injury severity (group membership). In fact, the preinjury family environment accounted for a larger amount of variance in outcome at 12 months post-injury than did injury severity. After controlling for injury severity and

demographics, family environment accounted for as much as 25% of the variance in cognitive outcome following TBI.

Furthermore, they found that family functioning moderated the effect of TBI in that children from families with above-average family functioning tended to experience a more rapid and complete recovery from TBI, while children from families with below-average family functioning tended to experience a slower and less complete recovery. Specifically, below average family functioning was associated with lower amounts of cognitive improvement over the course of the first year postinjury and worse cognitive outcomes at 12-months post injury. For example, the difference between the severe TBI and the OI groups in total recall scores on the CVLT at 12-months postinjury was directly proportional to measured family functioning. For children whose FAD scores reflected above-average family functioning (i.e., scores were 1 standard deviation below the mean, as lower scores on the FAD reflect better family functioning), the group difference was only 2.69 words. However, for children whose FAD scores were reflective of below-average family functioning (i.e., 1 standard deviation above the mean), the difference between the severe TBI and the OI groups was 9.23 words. Therefore, a difference of 2 standard deviations on the FAD resulted in a more "than 1 standard deviation increase in the discrepancy between the OI and severe TBI groups" in memory functioning (Yeates et al., 1997, p. 626).

The results of this study support the notion that family variables help to determine children's neurocognitive functioning following TBI and that the child's family environment moderates the impact of TBI (Yeates et al., 1997). Specifically, this study found that the deficits in memory functioning that are associated with severe TBI were cushioned by above-average family functioning and made worse by below-average family functioning (Yeates et al., 1997). Furthermore, their finding that environmental

measures such as family functioning accounted for at least as much, or more, variance in level of neurocognitive outcome than did measures of injury severity suggests that the child's eventual neurocognitive functioning following a TBI depends as much, if not more, on environmental influences than on injury-related variables (Yeates et al., 1997).

In a later report on findings extending this research by Yeates and colleagues, Taylor et al. (1999) examined whether postinjury family environment was related to concurrent child outcomes in TBI. They looked at three aspects of the family environment: family dysfunction, parental psychological distress, and injury-related family burden (Taylor et al., 1999). They assessed patients at baseline (shortly after injury), at 6 months postbaseline, and at 12 months postbaseline (Taylor et al., 1999). There were three groups of children included in the study: children with severe TBI, children with moderate TBI, and children with an orthopedic injury not involving insult to the CNS (Taylor et al., 1999). The orthopedic group was included in order to control for possible confounding variables such as proneness to accidents, the experience of hospitalization, and practice effects from repeated testing, as well as to examine possible differential consequences of TBI as opposed to non-CNS related injury (Taylor et al., 1999). As with the previous report, the measure of family functioning used in this study was the General Functioning scale of the FAD (Taylor et al., 1999). However, a much more comprehensive neurocognitive test battery was administered to the patients in this aspect of the study. The specific domains examined included global cognitive ability, language skills, perceptual-motor skills, memory, attention, academic achievement, school performance, behavior problems, child competence, and adaptive behavior.

They examined the influence of post-injury family status at the 6- and 12-month follow-ups on concurrent child outcomes via hierarchical linear regression (Taylor et al., 1999). This study found that these post-injury measures of family function predicted

concurrent child outcomes at both the 6- and 12-month follow-ups (Taylor et al., 1999). Higher levels of concurrent family functioning were associated with better child functioning, even after controlling for injury severity and pre-injury family functioning (Taylor et al., 1999). Furthermore, they found an interaction between group contrasts and family functioning, such that the group effect of severe TBI vs. orthopedic group interacted with the FAD-GF in predicting verbal memory, math skills, and teacher ratings of academic performance (Taylor et al., 1999). Specifically, this study found that the differences in outcomes between severe TBI and orthopedic injury in these domains were more pronounced in children from families with higher levels of dysfunction at both 6- and 12-months post baseline (Taylor et al., 1999).

Other studies have also found support for a link between family functioning and memory functioning among pediatric TBI patients. Max and colleagues used the McMaster Structured Interview of Family Functioning (Mc-SIFF), a clinical research interview based upon the MMFF, to assess family functioning (Max et al., 1999). The Mc-SIFF is used in order to obtain scores on a rating scale named the Clinical Rating Scale (CRS), which contains seven items corresponding to the seven domains of family functioning included in the MMFF (Max et al., 1999). They utilized the global score from the CRS in their analyses (Max et al., 1999). Max and colleagues (1999) assessed intellectual and memory functioning among children with severe traumatic brain injuries, mild traumatic brain injuries, and orthopedic injuries using the WISC-R and the WRAML. Specifically, they used a prorated PIQ score, a prorated VIQ score, and a FIQ score from a short form of the WISC-R and a Verbal Memory Index and Visual Memory Index from the WRAML in their analyses. Max and colleagues began with eight independent variables: family psychiatric history, duration of impaired consciousness, family functioning, lowest post-resuscitation score on the Glasgow Coma Scale (a

measure of responsiveness to stimuli following a TBI), neurological exam, "novel" post-injury psychiatric disorder, pre-injury psychiatric disorder, and socioeconomic status (Max et al., 1999).

The researchers found that intellectual and memory function outcome in pediatric brain injury was significantly related to a Psychosocial Disadvantage Factor that included family dysfunction (Max et al., 1999). Notably, this study found that family functioning, together with family psychiatric history, added significantly to SES in explaining cognitive outcomes two years after injury. While causation certainly could not be inferred from this cross-sectional study, the results do suggest that psychosocial disadvantage factors such as poor family functioning influence children's cognitive outcomes from TBI (Max et al., 1999). This study supported the findings of Yeates et al. and Taylor et al., and added findings related to general intellectual functioning as well.

A more recent study found similar results in the domains of attention/executive functioning. Nadebaum and colleagues investigated long-term attention/executive functioning among survivors of pediatric TBI (Nadebaum, Anderson, & Catroppa, 2007). Their study consisted of 54 children who had sustained a TBI and 17 healthy control subjects who were selected to match the TBI group as closely as possible in terms of age, gender, SES, and pre-injury abilities (Nadebaum, Anderson, & Catroppa, 2007). Family functioning was assessed using the Family Functioning Questionnaire (FFQ), which parents completed at baseline and five years post-injury (Nadebaum, Anderson, & Catroppa, 2007). They used four cognitive measures to assess the various subcomponents of EF included in Anderson's model (Anderson, 2002). These included Sky Search from the Test of Everyday Attention for Children (TEA-Ch) for attentional control (sustained attention), Score DT from the TEA-Ch for cognitive flexibility (divided attention), Block Design from the Wechsler Intelligence Scales for Children-III (WISC-III) for goal setting

(organization and perceptual reasoning), and the Processing Speed Index from the WISC-III (a composite of the Coding and Symbol Search subtests) for information processing (efficiency and speed of information processing). They also administered the Parent Form of the Behavior Rating Inventory of Executive Function (BRIEF), a rating scale that measures behavioral manifestations of executive dysfunction. The BRIEF was administered at baseline and five years post-injury, whereas the cognitive measures were only administered five years post-injury.

As with Taylor et al., Nadebaum and colleagues utilized hierarchical linear multiple regression analyses to identify factors that predicted EF outcome. They found that pre-injury family functioning was a significant predictor of Processing Speed Index scores, with higher scores associated with higher levels of family functioning. Family functioning also significantly predicted overall EF outcome (performance on the composite measure of EF), with better pre-injury family functioning again associate with better outcomes.

Summary.

Using different measures of family functioning, researchers have identified a protective influence on children's immediate and longer-term recovery from traumatic brain injury. Pre-injury family functioning, as reported at the time of injury, explained significant amounts of variance in executive functioning, memory, and intellectual outcomes at 6- and 12-months as well as 2- and 5-years postinjury (Max et al., 1999; Nadebaum, et al., 2007; Yeates, et al., 1997). Concurrent family functioning was also found to explain significant amounts of variance in memory and academic achievement at 6- and 12-months postinjury (Taylor et al., 1999). One interpretation of the findings of these studies is that the neurocognitive effects of TBI make these children more vulnerable to family influences than their peers who have not sustained a head injury

(Taylor et al., 1999). Also, it could be that families with higher levels of dysfunction lack the ability to adequately support the child's recovery from TBI, such that the child does not have enough opportunity or motivation necessary to perform the practice of cognitive skills that is necessary for a more complete neurocognitive recovery from TBI (Taylor et al., 1999). Another interpretation is that a positive family environment actually facilitates neural recovery (Taylor et al., 1999). This hypothesis has been supported in studies with animals, but has little empirical support to date from studies of human recovery of function (Taylor et al., 1999).

Family functioning and neurocognitive late effects in pediatric brain tumors.

In one of the only studies to examine the impact of family functioning on neurocognitive functioning among pediatric cancer patients, Carlson-Green and colleagues investigated the ability of family measures to predict the cognitive functioning of 63 children being treated for brain tumors (Carlson-Green et al., 1995). They used hierarchical multiple regression to determine whether or not family variables improved prediction of child outcomes over and above illness variables and covariates. Illness variables included measures of neurological symptoms and treatment severity. Family predictors included measures of maternal coping resources, family cohesion, family control, and family stressors. Cognitive outcome variables included a measure of intelligence and a measure of achievement. The covariates included in the model were time since diagnosis, SES, age at diagnosis, and parental marital status. In terms of cognitive outcomes, they found that family variables did explain a significant amount of variance in child intellectual outcome, with the most parsimonious model including both family (maternal coping resources) and illness (treatment severity) measures, as well as covariate measures (time since diagnosis, SES, and marital status). Family variables did

not account for any additional variance above illness factors in predicting child achievement outcomes.

Summary.

In summary, research from the fields of pediatric traumatic brain injury and pediatric brain tumors has shown that psychosocial variables such as family functioning moderate neurocognitive outcomes among these populations (Carlson-Green et al., 1995; Max et al., 1999; Nadebaum et al., 2007; Taylor et al., 1999; Yeates et al., 1997). Specifically, positive family functioning has been found to serve as a protective factor against the development of neurocognitive deficits in areas of neurocognitive functioning typically affected by TBI and brain tumors. This phenomenon has not yet been studied among survivors of pediatric ALL.

Chapter Three: Proposed Research Study

State of Problem

Some variables that seem to moderate neurocognitive outcome among survivors of pediatric ALL treated with chemotherapy-only have been identified, including gender, age at diagnosis, time since diagnosis, and socioeconomic status (Brouwers, 2005; Buizer et al., 2009; Moleski, 2000; Mulhern & Palmer, 2003; Patel & Carlson-Green, 2005; Peterson et al., 2008; Stehbens et al., 1994; Waber et al., 2011; Winick, 2011). However, much less is known about potential psychosocial moderators such as family functioning (Anderson & Kunin-Batson, 2009; Patel & Carlson-Green, 2005). Evidence from the pediatric traumatic brain injury and pediatric brain tumor populations suggests that positive family functioning serves as a protective factor for neurocognitive outcomes of children who survive these conditions (Carlson-Green et al., 1995; Max et al., 1999; Nadebaum et al., 2007; Taylor et al., 1999; Yeates et al., 1997). No research has been done to see whether positive family functioning similarly moderates the effects of CNS-directed chemotherapy on the neurocognitive functioning of survivors of pediatric ALL. Identification of all possible protective factors for neurocognitive outcomes among survivors of pediatric ALL is necessary in order to design, research, and implement effective interventions in order to lessen the prevalence of neurocognitive late effects among this population.

Statement of Purpose

The purpose of this proposed study is to examine the effect of family functioning upon neurocognitive outcome among survivors of pediatric ALL treated with chemotherapy. Specifically, the proposed study seeks to determine if positive family functioning serves as a protective factor against the neurocognitive deficits commonly

seen in this population. Based upon a multidimensional model of attention and Anderson's model of executive function (EF), four subcomponents of attention and four subcomponents of EF will be examined (Anderson, 2002). The attention subcomponents are: selective, divided, sustained, and shifting. The EF subcomponents are: cognitive flexibility (working memory), goal setting (planning), attentional control (inhibition), and information processing (processing speed). It is hypothesized that family functioning will add to such moderating factors as age at diagnosis, gender, time since diagnosis, and SES in predicting neurocognitive outcome in the domains listed above.

Research Questions and Hypotheses

Research question 1.

Does positive family functioning protect against deficits in attention among survivors of pediatric ALL, specifically in the subdomains of selective attention, divided attention, sustained attention, and shifting attention, and as reported by parents?

Hypothesis 1.

Differences in family functioning will account for a significant amount of the variance in performance on a task of selective attention for survivors of pediatric ALL but not for healthy controls.

Differences in family functioning will account for a significant amount of the variance in performance on a task of divided attention for survivors of pediatric ALL but not for healthy controls.

Differences in family functioning will account for a significant amount of the variance in performance on a task of sustained attention for survivors of pediatric ALL but not for healthy controls.

Differences in family functioning will account for a significant amount of the variance in performance on a task of shifting attention for survivors of pediatric ALL but not for healthy controls.

Differences in family functioning will account for a significant amount of the variance in scores on parent ratings of inattention for survivors of pediatric ALL but not for healthy controls.

Rationale.

Survivors of pediatric ALL treated with chemotherapy have been found to have deficits in selective, divided, sustained, and shifting attention and in parent ratings of attention (Anderson & Kunin-Batson, 2009; Ashford et al., 2010; Bisen-Hersh et al., 2011; Butler & Copeland, 2002; Carey et al., 2008; Harila et al., 2009; Kingma et al., 2002; Lesnik et al, 1998; Reddick et al., 2006). Family functioning has been found to moderate neurocognitive outcome in survivors of pediatric traumatic brain injury and brain tumor in domains sensitive to insult in those populations (Carlson-Green et al., 1995; Max et al., 1999; Nadebaum et al., 2007; Taylor et al., 1999; Yeates et al., 1997). It is expected that family functioning will similarly moderate neurocognitive outcomes in the ALL population in attention, a domain sensitive to insult in this population. Furthermore, it is expected that positive family functioning will serve as a protective factor against the development of attention problems among survivors of pediatric ALL. It is thought that higher functioning families may be better able to manage survivors' neurocognitive late effects, for example, by providing opportunities for the survivor to practice and strengthen the attentional skills that have been negatively impacted by the chemotherapy treatment. In alignment with Rose and colleagues' conceptualization of protective factors as operating only in instances of adversity, it is expected that children in the healthy control group, who have not been exposed to adversity in the form of CNS

prophylaxis, will not demonstrate the same relationship between family functioning and performance on measures of attention (Rose, Holmbeck, Coakley, & Franks, 2004).

Research question 2.

Does positive family functioning protect against deficits in executive functioning among survivors of pediatric ALL, specifically in the subdomains (areas) of cognitive flexibility (working memory), goal setting (planning), attentional control (inhibition), information processing (processing speed) and as reported by parents?

Hypothesis 2.

Differences in family functioning will account for a significant amount of the variance in performance on a task of cognitive flexibility (working memory) for survivors of pediatric ALL but not for healthy controls.

Differences in family functioning will account for a significant amount of the variance in performance on a task of goal setting (planning) for survivors of pediatric ALL but not for healthy controls.

Differences in family functioning will account for a significant amount of the variance in performance on a task of attentional control (inhibition) for survivors of pediatric ALL but not for healthy controls.

Differences in family functioning will account for a significant amount of the variance in performance on a task of information processing (processing speed) for survivors of pediatric ALL but not for healthy controls.

Differences in family functioning will account for a significant amount of the variance in scores on parent ratings of executive functioning for survivors of pediatric ALL but not for healthy controls.

Rationale.

Survivors of pediatric ALL treated with chemotherapy have been found to have deficits in executive functioning, including working memory, inhibition, processing speed, and planning, and on parent ratings of executive functioning (Ashford et al., 2010; Buizer et al., 2009; Harila et al., 2009; Jansen et al., 2008; Kingma et al., 2002; Lesnik et al., 1998; Waber et al., 1995). Family functioning has been found to moderate neurocognitive outcome in survivors of pediatric traumatic brain injury in the domain of executive functioning (Nadebaum et al., 2007). It is expected that a similar moderating effect of family functioning on executive functioning will exist among the ALL population. Moreover, it is expected that positive family functioning will serve as a protective factor against the development of deficits in executive functioning among survivors of pediatric ALL. As such, it is expected that children in the healthy control group, who have not been exposed to adversity in the form of CNS prophylaxis, will not demonstrate the same relationship between family functioning and performance on measures of attention (Rose et al., 2004).

Method

Participants.

Participants in this study will include 85 children and adolescents who have completed chemotherapy-only treatment for ALL and 85 healthy control participants, equaling a total of 170 participants (N = 170). In order to match epidemiological figures of ALL set forth by McNeil et al. (2002), the groups will be comprised of the following percentages: 57% male, 43% female; 83% white, 7% black, 9% other. Control participants will be recruited from the same zip codes as the survivors in order to minimize between-groups differences in socioeconomic status. The rationale for including a healthy control group was to permit investigation of family functioning as protective factor, that is, as a moderator of outcome in the presence of adversity (Rose et

al., 2004). All participants will be within the ages of 8 and 16. This age range was chosen so that all participants in the study could be evaluated using the same battery of neuropsychological tests.

Inclusion criteria will be: (i) aged 8 to 16 years throughout the length of the study, (ii) post-treatment and having been designated as survivors of pediatric Acute Lymphoblastic Leukemia (ALL) by the LIVESTRONG Survivorship Center at Dell Children's Medical Center in Austin, Texas, and (iii) English-speaking. Patients are typically designated as survivors after completion of treatment and one year of being cancer-free. Individuals meeting school criteria as having a visual or auditory impairment or attention difficulties such as attention-deficit/hyperactivity disorder (ADHD) will be excluded from the study. Additionally, individuals who are undergoing treatment for ALL at the time of the study, who underwent a bone-marrow transplant or cranial radiation therapy, had a recurrence of cancer, or who had impaired global cognitive functioning (e.g. mental retardation) will not be included in this investigation. Power analyses were conducted to determine the number of participants needed to detect a significant effect for the multiple regression analyses. A sample size of 170 was determined to be the minimum number needed to detect a significant effect for both tests.

Instruments.

Participants will be administered measures of attention and executive functioning and their parents will be asked to complete rating forms about their attention and executive functioning. Additionally, one parent of each child involved in the study will complete a measure of family functioning.

Attention measures.

Test of Everyday Attention – Children's Version (TEA-Ch). The Test of Everyday Attention for Children (TEA-Ch; Manly, Robertson, Anderson, & Nimmo-Smith, 1999)

is a children's adaptation of the adult Test of Everyday Attention (TEA). It has been used in research with males with Fragile X syndrome, girls with Turner's syndrome, and children with head injury, ADHD, and learning disabilities (Baron, 2004). The full TEA-Ch is comprised of 9 subtests and a full administration takes approximately 1 hour. However, there is also a four-subtest screener version that takes 20-25 minutes to administer and assesses each of the four dimensions of attention (selective, divided, sustained, and shifting). The normative sample for the TEA-Ch was comprised of 293 Australian children and adolescents between the ages of 6 years, 7 months and 16 years, 11 months and included equal numbers of males and females. The sample was divided into six age bands, with 29 to 58 children in each age band. Reported test-retest reliabilities for the TEA-Ch range from .57 to .87, with percentage agreement values ranging from 71% to 76% (Manly et al, 1999). A structural equation modeling study involving the normative sample resulted in a three-factor model of sustained attention, attentional control/switching, and selective attention (Manly et al., 2001).

The four-subtest screener version of the TEA-Ch will be used in this study to assess the four subdomains of attention described previously. The specific subtests that will be administered are: Sky Search, Score!, Creature Counting, and Sky Search DT. Sky Search is a measure of selective attention that requires the subject to filter information in order to detect relevant information while rejecting or inhibiting distracting information (Baron, 2004; Manly et al., 1999). The reported test retest correlation coefficient from the normative sample for this subtest was 075. Score! is a measure of sustained attention that requires the subject to count tones played on an audio recording and report the correct number of tones at the end of each round (Baron, 2004; Manly et al., 1999). The reported percentage agreement from the normative sample for this subtest was 76.2%. Creature Counting is a measure of switching attention that

requires the subject to count stimuli according to visual cues indicating for them to count either upwards or downwards (Baron, 2004; Manly et al., 1999). There are two scores available for this subtest: an accuracy score and a timing score. For the proposed study, the accuracy score will be used as a measure of switching attention. The reported test retest correlation coefficient from the normative sample for this measure was 0.71. Sky Search DT is a measure of divided attention that requires the subject to circle certain stimuli while also keeping count of auditory tones (Baron, 2004; Manly et al., 1999). The reported test retest correlation coefficient from the normative sample for this subtest was 0.81.

Behavior Assessment System for Children – Second Edition (BASC-2). The Behavior Assessment System for Children – Second Edition (BASC-2; Reynolds & Kamphaus, 2004) is a comprehensive set of rating scales and forms that assess behavioral and emotional functioning of children and adolescents, including teacher, parent, and self-report versions. There are various forms of each of the three versions for use with different age groups, ranging from 2 years old through college age. For this study, the child (ages 6 to 11) and adolescent (ages 12 to 21) forms of the Parent Rating Scales (PRS) will be used. These scales contain a number of items (134-160) that describe specific patterns of behavior and are rated on a four-point frequency scale ranging from "never" to "almost always". The child and adolescent forms of the BASC-2 PRS were each standardized on a sample of 1,800 individuals representative of the U.S. population in terms of socioeconomic status, race/ethnicity, and geographic region according to figures from the March 2001 Current Population Survey. For the purposes of this study, the "Attention Problems" scale from the PRS will be used in assessing parental report of children's attentional abilities. Reported coefficient alpha reliabilities from the normative sample for the attention problems scale on the child and adolescent forms of the PRS

range from .85 to .88. Adjusted test-retest reliability coefficients for this scale are 0.81 for the adolescent form and 0.85 for the child form.

Executive functioning measures.

Delis-Kaplan Executive Function System (D-KEFS). The Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) is a standardized battery of tests that measure a variety of executive functions in people age 8 through 89 years. The D-KEFS was standardized on a nationally representative sample of 1750 people ages 8-89 years. The sample was stratified in regards to age, sex, race/ethnicity, years of education, and geographic region using figures from the 2000 U.S. Census. For this study, the following two subtests of the D-KEFS will be administered: the D-KEFS Tower Test and the D-KEFS Color-Word Interference Test. The D-KEFS Tower Test is a measure of planning (Baron, 2004; Delis et al., 2001). Specifically, the Total Achievement scaled score will be used as a measure of planning. Reported internal consistency values for this measure for children ages 8-16 ranged from 0.43 to 0.84. The reported test-retest reliability coefficient for this age group was 0.51. The D-KEFS Color-Word Interference Test is a measure of inhibition (Baron, 2004; Delis et al., 2001). Specifically, the Trial 3: Inhibition time scaled score will be used as a measure of inhibition. The reported test-retest reliability coefficient for this measure for children ages 8-16 was 0.90.

Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV). The Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; Wechsler, 2003) is a widely used measure of cognitive ability. It is comprised of fifteen subtests, ten in the core battery and five that are supplemental. It is designed for children age 6:0 through 16:11 and takes 65 to 80 minutes to administer in full. The WISC-IV yields a measure of global cognitive ability, the Full Scale IQ (FSIQ), as well as four composite scores: the

Verbal Comprehension Index (VCI), the Perceptual Reasoning Index (PRI), the Working Memory Index (WMI), and the Processing Speed Index (PSI). The WISC-IV was standardized on a nationally representative sample of 2,200 children, stratified according to March 2000 U.S. Census data along the variables of age, sex, race/ethnicity, parent education level, and geographic region.

For the purposes of this study, four subtests of the WISC-IV will be administered to participants. These are the Digit Span and Letter-Number Sequencing subsets, which together comprise the WMI, and the Symbol Search and Coding subtests, which together comprise the PSI. Digit Span consists of two parts, Digit Span Forward (DSF) and Digit Span Backward (DSB). On DSF, the subject is required to repeat verbatim numbers presented to them orally. On DSB, the subject has to repeat numbers in the reverse order of that in which they are presented. Scores on these two components are combined to produce a total Digit Span scaled score. The reported overall average reliability coefficient from the normative sample for this subtest was 0.87. Letter-Number Sequencing requires the subject to listen to strings of mixed numbers and letters and to repeat the string with numbers first, in numerical order, followed by letters in alphabetical order. The reported overall average reliability coefficient from the normative sample for this subtest was 0.90. Symbol Search requires the subject to visually scan a group of stimuli and indicate whether or not a target stimulus is present. The reported overall average reliability coefficient from the normative sample for this subtest was 0.79. Coding requires the subject to copy symbols paired with shapes or numbers within a given time limit. The reported overall average reliability coefficient from the normative sample for this subtest was 0.85.

Behavior Rating Inventory of Executive Function (BRIEF). The Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000)

consists of two forms, a parent questionnaire and a teacher questionnaire. Each form consists of 86 items scored on a 3-point scale (Never, Sometimes, Often). It takes approximately 10 to 15 minutes to complete and can be used with children ages 5 to 18 years. The BRIEF assess eight subdomains of executive function: inhibition, shifting, and emotional control, which together comprise a broader composite score called the Behavioral Regulation Index (BRI), and initiation, working memory, planning/organizing, organization of materials, and monitoring, which together comprise the Metacognition Index (MI) composite. The BRI and MI are then combined to produce the overall Global Executive Composite (GEC) score. For this study, the GEC from the parent form of the BRIEF will be used as a measure of overall executive functioning as reported by parents. The parent form of the BRIEF was standardized on a sample of 1,419 parents from urban, suburban, and rural areas of Maryland. The sample was representative of 1999 U.S. Census data in regards to gender, socioeconomic status, ethnicity, age, and geographical population density. The reported Cronbach's α for the GEC on the Parent Form of the BRIEF is 0.97. Reported test-retest reliability for the GEC is 0.91.

Family functioning measure.

Family Assessment Device (FAD). Family functioning will be measured using the Family Assessment Device (FAD), a well-established self-report measure of family functioning based upon the McMaster Model of Family Functioning. It consists of six scales representing the six dimensions of family functioning included in the MMFF, as well as a General Functioning Scale (GFS) that provides a measure of overall family functioning based upon the other six scales. The FAD consists of 60 items about families, and asks the rater to indicate how much each item describe their family's functioning on a 4-point Likert scale that ranges from strongly agree to strongly disagree. The FAD

takes approximately 20 minutes to complete and can be administered to any family member over the age of 12. Higher scores on the scales of the FAD indicate higher levels of family dysfunction. It will be administered one adult from each family participating in the study. For the purposes of this study, the FAD GFS will be used as a measure of overall family functioning. Kabacoff and colleagues conducted a study of the psychometric properties of the FAD among nonclinical (n = 627), psychiatric (n = 1,138) and medical (n = 298) samples (Kabacoff, Miller, Bishop, Epstein, & Keitner, 1990). Cronbach alphas for the GFS among these samples were .83, .84, and .86, respectively.

Procedure.

Approval by human subjects committee.

This study will be conducted in compliance with the ethical standards set forth by the American Psychological Association and The University of Texas at Austin. All research materials will be approved prior to data collection by the Departmental Review Committee within the Department of Educational Psychology and by the Institutional Review Board of The University of Texas at Austin.

Recruitment of participants.

Participants for the experimental group will be recruited through the LIVESTRONG Survivorship Center in Austin, Texas. Children designated by their oncologists as survivors of pediatric ALL and who meet the inclusion criteria will be invited to participate in the study. All such children and adolescents, regardless of length of survivorship status, will be invited to participate in order to maximize the potential sample size. Control participants will be solicited through local school districts. With the permission of district officials, advertisements will be placed on bulletin boards around the schools, in newsletters sent home to parents, and on school websites. As an incentive for participation in the study, each child in the control group will be entered into a raffle.

Consent.

Participation in the study will be voluntary and participants will be able to discontinue participation at any time, for any reason. Guardians of all participants will receive a copy of the consent form and will have the chance to discuss any concerns with the researcher. Participants themselves will be given assent forms and the chance to discuss any concerns with the researcher as well.

Data collection.

Children who assent to participate in the study, whose parents give consent for participation, and who meet inclusion criteria will be participants in this study. Once informed consent and assent are obtained, the parent or guardian of the child will schedule an appointment with the principal investigator for the child to participate in a neuropsychological evaluation. Children in the survivorship group who are due for their initial neuropsychological evaluation upon entering survivorship or those who are due for a neuropsychological re-evaluation will take part in the full neuropsychological evaluation given as part of their routine clinical care. Control participants and those survivors not due for evaluation or re-evaluation will be administered a short neuropsychological battery comprised only of the measures being used as part of the proposed study. All evaluations will take place in a quiet, private room in the Children's Blood and Cancer Center (CBCC) in the Specially for Children building at Dell Children's Medical Center in Austin, Texas. The child will engage in a one-on-one neuropsychological evaluation with the principal investigator for approximately 90 minutes (research-only battery) or 330 minutes (full battery) while their parent/guardian fills out parent forms (BRIEF, BASC, FAD) in a waiting room. The child will be allowed to take breaks as needed during the testing session.

Data Analysis and Expected Results

The purpose of this study is to examine the relationship between family functioning and concurrent neurocognitive functioning among survivors of ALL treated with chemotherapy as compared to a group of healthy controls. Data will be analyzed using a multiple regression analysis.

Preliminary analyses.

Two power analyses were conducted using G*Power software to determine the number of participants needed to detect a significant effect (Faul, Erdfelder, Buchner, & Lang, 2009). A power analysis for detecting a significant R2 change requires 55 participants to obtain a moderate effect size (f2 = .15) at the level of power of .80 and an alpha of .05 with one independent variable. Because the proposed study requires separate regression analyses for the ALL group and the control group, a total of 110 participants would be needed. In addition, a power analysis for detecting an overall significant R2 deviation from zero with four predictor variables was conducted, in accordance with research convention. For four predictor variables, 85 subjects per analysis are needed to obtain a moderate effect size (f2 = .15) at the level of power of .80 and with an alpha of .05. Therefore, 170 total participants are needed.

Descriptive statistics, including means, standard deviations, ranges, and minimum and maximum values, will be computed and analyzed for each variable. Variables will also be checked for normality and data will be checked for outliers. Linearity will be determined based on scatterplots and normal distribution of residuals will be confirmed using a residual and predicted value plot. Data will also be tested for multicollinearlity.

Tests of research questions.

Sequential, or hierarchical, multiple regression analyses will be conducted to examine the relationship between family functioning and neurocognitive functioning,

controlling for age at diagnosis and time since diagnosis within the ALL group and for gender and SES in both control and ALL groups (Huck, 2008). Data for the ALL group and the control group will be examined using separate analyses. Using a sequential regression, the control variables will be entered first. For the experimental group, these are: age at diagnosis, gender, time since diagnosis, and SES; for the control group they are age, gender, and SES. These will be followed by family functioning as a predictor variable for the neurocognitive outcome measures. The p-value associated with the change in R2 will be examined to determine if family functioning explains a significant amount of variance in neurocognitive outcome, even after controlling for demographic and treatment-related variables. A change in R2 associated with an alpha of less than .05 will be considered significant.

Hypothesis 1.

Family functioning is expected to explain a significant amount of variance in performance on a task of selective attention, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning is not expected to account for a significant amount of additional variance in performance on a task of selective attention beyond that accounted for by demographic variables.

Family functioning is expected to explain a significant amount of variance in performance on a task of divided attention, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning is not expected to account for a significant amount of additional variance in performance on a task of divided attention beyond that accounted for by demographic variables.

Family functioning is expected to explain a significant amount of variance in performance on a task of sustained attention, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning is not expected to account for a significant amount of additional variance in performance on a task of sustained attention beyond that accounted for by demographic variables.

Family functioning is expected to explain a significant amount of variance in performance on a task of switching attention, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning is not expected to account for a significant amount of additional variance in performance on a task of switching attention beyond that accounted for by demographic variables.

Family functioning is expected to explain a significant amount of variance in scores on parent ratings of attention, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning is not expected to account for a significant amount of additional variance in scores on parent ratings of attention beyond that accounted for by demographic variables.

Hypothesis 2.

Family functioning is expected to explain a significant amount of variance in performance on a task of cognitive flexibility (working memory), above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning is not expected to account for a significant amount of additional variance in performance on a task of cognitive flexibility (working memory)beyond that accounted for by demographic variables.

Family functioning is expected to explain a significant amount of variance in performance on a task of goal setting (planning), above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning is not expected to account for a significant amount of additional variance in performance on a task of goal setting (planning) beyond that accounted for by demographic variables.

Family functioning is expected to explain a significant amount of variance in performance on a task of attentional control (inhibition), above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning is not expected to account for a significant amount of additional variance in performance on a task of attentional control (inhibition) beyond that accounted for by demographic variables.

Family functioning is expected to explain a significant amount of variance in performance on a task of information processing (processing speed), above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning is not expected to account for a significant amount of additional variance in performance on a task of information processing (processing speed) beyond that accounted for by demographic variables.

Family functioning is expected to explain a significant amount of variance in scores on parent ratings of executive functioning, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning is not expected to account for a significant amount of additional variance in scores on parent ratings of executive functioning beyond that accounted for by demographic variables.

Chapter Four: Discussion

Limitations

The proposed study has several limitations. First of all, the measure of family functioning that is proposed is not specific to the ALL population. As such, it may be inadequate to capture the experiences of this population. However, it has a long tradition of use in chronically ill populations. Secondly, the sample included in the study might be biased towards those children and families who have the means and ability to travel to the hospital for testing. As such, the socioeconomic status of participants might not be truly representative of the ALL population as a whole. In addition, the proposed study, being cross-sectional as opposed to longitudinal, does not follow children from diagnosis through survivorship. This, as well as the lack of random assignment, precludes the ability to infer causation from the results. Furthermore, there is the potential for children who have received previous evaluations to demonstrate practice effects on neuropsychological testing. Since more of the experimental than control participants will be likely to have had previous neuropsychological testing, this could confound the results of the analyses.

The proposed study is also limited by the inclusion of only one family member's perspective of family functioning. Ideally, the FAD would have been completed by each member of every family participating in the study and a family mean would have been calculated, per the recommendation of the developers of the FAD (Alderfer et al., 2009). However, this was deemed to be impractical in the current proposed study, as it would have limited the sample to only those children able to complete the FAD (i.e., over the age of 12 years). Furthermore, differences in family constellations could have introduced additional complexities in the comparison of functioning between families, as the number of people rating family functioning would have varied based on the number of people in

each family. Finally, it is limited by the lack of inclusion of an interview-based measure of family functioning. Within the field of family assessment, it is considered ideal to obtain both "insider" and "outsider" views of the family's functioning (Carlson, 2003). "Insider" views are those reported by the family members themselves, such as on self-report measures like the FAD. "Outsider" views are those of clinicians or other observers of the family, and may be obtained via structured interview of the family or a clinical rating scale. Inclusion of such a measure in the proposed study was considered, but it was deemed impractical to require this additional time and energy from participants, especially those in the control group.

Summary and Implications

The proposed study seeks to fill a gap in the literature on the neurocognitive late effects of acute lymphoblastic leukemia by investigating the moderating effect of family functioning on attention and executive functioning in survivors of ALL treated with chemotherapy. It is expected that positive family functioning will serve as a protective factor against late effects in these domains of neurocognitive functioning for ALL survivors. If so, this would have important implications for the survivors and their families. Such findings would inform efforts to design interventions for this population. If it is found that family functioning moderates neurocognitive outcomes for survivors of pediatric ALL, then survivors from families with lower levels of functioning could be identified early through screening measures and their families could receive targeted interventions aimed at improving family functioning and thus survivor outcomes. In the modern age of managed care and cost cutting measures, empirically supported interventions are necessary. The proposed study could potentially add to the empirical base in support of family-level intervention within the ALL population.

Future research could also expand upon the current proposed study by investigating the bidirectional interactions between family functioning and neurocognitive functioning in determining quality of life among survivors of pediatric ALL and their families. The proposed study examines the relationship between family functioning and neurocognitive functioning in only one direction, but it is likely that the relationship between these two variables is more complex than the current model would suggest. Specifically, the neurocognitive functioning of the survivor may also impact the functioning of the family, and both of these factors could in turn influence the quality of life of survivors and their families. A model of survivorship based upon this reciprocal relationship between the survivor and their family has been proposed by other researchers and evidence has been found to support it in the pediatric brain tumor population (Hocking et al., 2011; Peterson & Drotar, 2006). As the relationship between family functioning and neurocognitive functioning among survivors of ALL has never been investigated, it was beyond the scope of this proposed study to investigate the more sophisticated model of survivorship proposed by Peterson and Drotar. However, the expected results from this proposed study would give support to the need to investigate the applicability of this model to the ALL population.

This study has the potential to be the first step in a rich and meaningful line of research focused on family functioning, neurocognitive functioning, and quality of life among survivors of pediatric ALL. Such research is crucial if we are to fulfill the goal, described by Bisen-Hersh et al. (2011), of decreasing the late effects of cancer treatment so that eventually a child's fight with cancer will end upon the achievement of remission rather than continuing into survivorship in the form of neurocognitive late effects.

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